Consultant360 Multidisciplinary Medical Information Network

CASE IN POINT

PEER REVIEWED

Refractory Kawasaki Disease Complicated By Urinary Tract Infection

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A 3-year-old African American girl presented to the emergency department (ED) with 4 consecutive days of fever (maximum temperature of 38.8 °C), a diffuse papular rash, conjunctival injection, and skin peeling on her palms, soles, and genital areas. Her fever persisted despite the administration of twice-daily acetaminophen during this illness.

The girl's history was significant for eczema, scarlet fever, and intussusception that did not require surgical intervention. Her surgical history was otherwise insignificant.

Examination in the ED revealed prominent bilateral cervical lymphadenopathy with a tender, mobile lymph node in the right anterior cervical chain that measured 2.5 cm in diameter. Her oral mucosa was erythematous with cracked lips and prominent papillae. She had mild conjunctival injection with perilimbic sparing. Skin examination findings were significant for a rough, erythematous, raised rash on her chest and back, along with desquamation of her palms, soles, and genital area.

Immediate evaluation included a rapid streptococcal test, complete blood cell count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), comprehensive metabolic panel (CMP), peripheral blood culture, urinalysis, and urine culture. The urine sample was obtained via a clean-catch and showed positive results for leukocyte esterase (1+) and nitrites, with 6 to 10 white blood cells (WBCs) per high-power field. CBC results were significant for a hemoglobin level of 9.9 g/dL, a WBC count of 11,200/μL, and a platelet count of 330 × 10^3/μL. CRP and ESR were elevated to 119.6 mg/L and 66 mm/h, respectively. CMP results were unremarkable. The rapid streptococcal test results were negative.

Due to her history of fever, oral mucosal findings, rash, peripheral peeling, conjunctival injection, and cervical lymphadenopathy, developing Kawasaki disease (KD) was suspected, and she was admitted to the hospital under the hospitalist service for observation. Given that her urinalysis sample was obtained via a clean-catch, there was concern for contamination and she was not immediately started on a course of antibiotics.

On her first day of admission, the patient had her fifth consecutive day of fever (**Figure 1**) and received a diagnosis of KD, since she had now fulfilled all 5 of the following diagnostic criteria: bilateral bulbar conjunctival injection, oral mucous membrane changes, peripheral extremity changes, polymorphous rash, and cervical lymphadenopathy (with at least 1 lymph node greater than 1.5 cm in diameter).[1,2] She was given intravenous immunoglobulin (IVIG, 2 g/kg) and started on oral high-dose aspirin (25 mg/kg every 6 hours). An initial echocardiogram showed normal heart function and no coronary artery dilation.

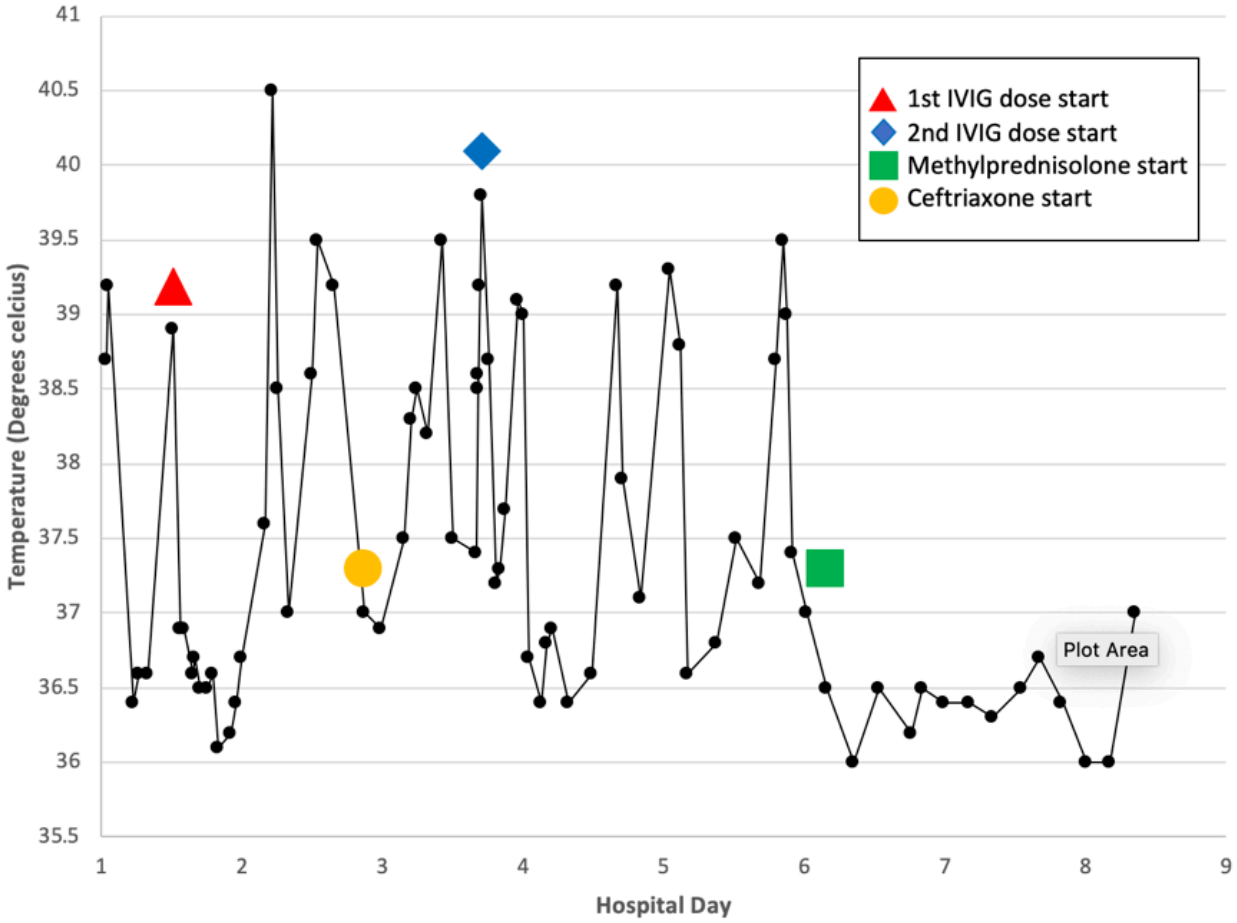

Figure 1. *Scatter plot demonstrating the patient's persistent fever in the setting of 2 IVIG treatments and ceftriaxone, then normalization of her temperature after the start of methylprednisolone.*

Her fever persisted during treatment, but then 33 hours after IVIG administration (on hospital day 3), she had a temperature of 39.5°C with an increase in CRP to 14.21 mg/L. At this time, urine culture had also grown more than 100,000 colony-forming units of *Escherichia coli*. It was unclear whether her persistent fever was due to KD that was unresponsive to IVIG treatment or if it was secondary to a urinary tract infection (UTI), so she was started on a course of empirical ceftriaxone (50 mg/kg intravenously every 24 hours) to treat the potential UTI.

After the first dose of ceftriaxone, a second urinalysis and urine culture sample was obtained via catheterization (the results of which were ultimately negative), and renal ultrasonography was performed (findings of which were negative for pyelonephritis and anatomic abnormalities). Even in the setting of negative renal ultrasonography findings, pyelonephritis could not be ruled out, given her age (older than 2 years), positive urine culture results, and febrile illness on presentation.[3] A second dose of IVIG, 2g/kg, was then given in the setting of persistent fever.

After her second dose of IVIG, a CBC was obtained, the results of which showed a drop in her hemoglobin level to 6.5 g/dL (**Figure 2**), with an inappropriately normal reticulocyte percentage

of 1.9%. Her CRP level had also climbed to 19.06 mg/L. The decision was made to refrain from giving a packed red blood cell transfusion, since she was nontoxic in appearance with no signs of active bleeding. We felt that her new-onset anemia likely was due to inflammation from active KD as opposed to hemolytic anemia secondary to IVIG therapy.

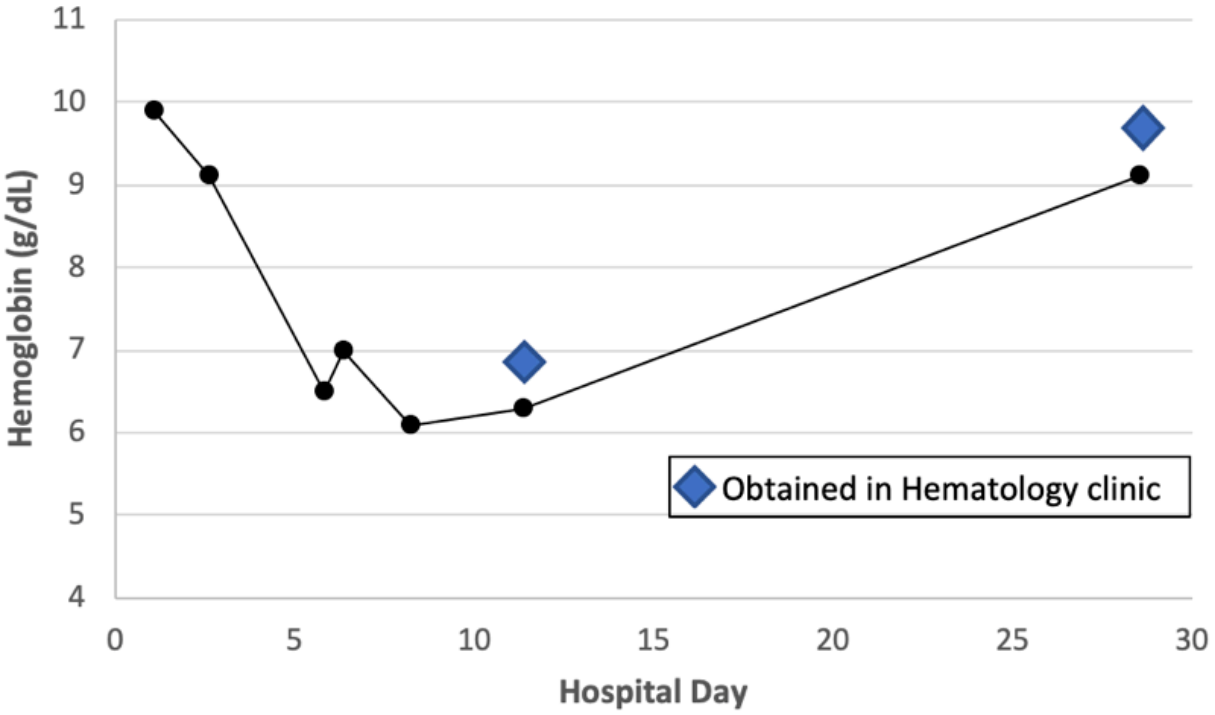

Figure 2. *Scatter plot demonstrating the patient's decreasing hemoglobin level during hospitalization (until day 8) and subsequent recovery at serial follow-up appointments.*

Eleven hours after completing her second IVIG dose (on hospital day 5), the patient had yet another fever, with a temperature to 38.8°C. A CBC was obtained, the results of which were significant for a hemoglobin level of 6.5 g/dL, a WBC count of 25,000/μL, and a platelet count of $415 \times 10^3/\mu$L. Results of a CMP at that time showed a sodium level of 131 mEq/L and an albumin level of 2.7 g/dL. She also had an elevated lactate dehydrogenase level of 255 U/L and normal bilirubin level of 0.8 mg/dL. Given the apparent treatment failure, she was started on a course of methylprednisolone (30 mg/kg every 24 hours) and completed 3 days of this treatment without any further fever or other adverse events.

Prior to discharge, on hospital day 8, a second echocardiogram again demonstrated normal heart function and no coronary artery dilation. She continued to have normocytic anemia with a hemoglobin level of 6.1 g/dL, but her reticulocyte percentage had improved to 3.9%, suggesting active red blood cell production.

Upon discharge, the girl was transitioned to low-dose aspirin (5 mg/kg orally every 24 hours) and cefdinir (14 mg/kg orally every 24 hours) to complete a 10-day course of treatment for her UTI. She was scheduled for close follow-up with a hematologist to repeat laboratory tests and a cardiologist to repeat echocardiography in 2 and 6 weeks.

At hematology follow-up 3 days after discharge, the girl's hemoglobin level was 6.3 g/dL with a reticulocyte percentage of 13%. These laboratory tests were repeated 2 weeks later, at which time her hemoglobin level was 9.1 g/dL with reticulocyte percentage of 2.1%. At cardiology follow-up at 2 and 6 weeks after discharge, her echocardiograms continued to demonstrate normal heart function with no dilation of her coronary arteries. Her low-dose aspirin regimen was discontinued at this time.

DISCUSSION

KD is a medium-sized vasculitis that primarily affects children younger than 5 years old. It is classically characterized by a fever lasting for 5 or more days and meeting 4 of the 5 following criteria: erythema and edema of the hands and feet followed by membranous desquamation of the fingers; polymorphous exanthem; bilateral painless bulbar conjunctival injection without exudate; changes in the lips and oral cavity; and cervical lymphadenopathy greater than 1.5 cm that is usually unilateral.[1,2] Although the cause of KD is unknown, it is theorized to be an autoimmune disease triggered by an infectious or environmental insult in a genetically susceptible child.[2]

Our patient presented with the classic findings of KD; however, she had a concurrent bacterial pyuria secondary to a UTI with *E coli*. Pyuria in the setting of KD is quite common, with a reported occurrence rate of 30% to 80% in the disease population.[4] Patients with pyuria typically have a more severe inflammatory reaction with a prolonged ESR, an elevated CRP level, an elevated serum alanine aminotransferase, along with a longer duration of fever after therapy with high-dose IVIG and aspirin.[5]

Among patients with KD and pyuria, sterile pyuria is most common. One study showed that the occurrence rate of pyuria in children with KD was 29.5%; in those with urine culture tests, 45.3% had sterile pyuria and only 10.7% had a bacterial pyuria.[6] The clinical phenotypes between these groups did not differ in regard to clinical presentation, markers of inflammation, duration of fever, and response to treatment.[6]

The results of another study demonstrated that the presence of infection (viral or bacterial) does not increase the risk of adverse coronary artery outcomes.[7] Even so, bacterial infections can be detrimental in this setting, since their presence can prompt the initiation of antibiotics instead of treatment for KD. Downie and colleagues found that patients who received delayed or no treatment with IVIG were also more likely to be administered antibiotics during the acute KD

illness.[8] Antibiotics were given in 47% of those who were treated promptly, 58% of those who had delayed treatment, and 57% of those who were not treated.[8]

Patients with KD may also have subclinical or clinically apparent renal injuries such as tubulointerstitial nephritis, acute nephritic syndrome, or nephrotic syndrome, necessitating further workup of urinary tract abnormalities.[4] Our patient had negative bacterial urine cultures 2 days after initiation of ceftriaxone, and subsequent renal ultrasonography findings were normal.

The most dangerous complication of KD is coronary aneurysms, which occur in 25% of untreated children but only 4% of children treated with IVIG.[2] Aneurysms also occur more often in KD that is refractory to IVIG. In a retrospective survey of 378 children with KD evaluated at 9 clinical centers across North America during a 15-month period, 2.8% of patients with normal baseline echocardiograms developed coronary artery abnormalities after IVIG treatment.[9] Of these patients, treatment failure occurred in 1.4% of those who became afebrile after IVIG and in 12.2% of those with persistent or recrudescent fever after IVIG.[9]

Our patient had persistent fever, elevated inflammation markers, and hemolytic anemia (a reported adverse effect of IVIG[2]) in the setting of 2 IVIG treatments and 3 doses of intravenous methylprednisolone. Given this degree of inflammation, we expected her to demonstrate coronary artery abnormalities; however, she had normal coronary artery findings at presentation and at subsequent follow-up visits at 2 and 6 weeks after discharge.

The demographics of our patient may have served as a protective mechanism against coronary artery disease. Being African American and being between the ages of 1 and 5 years have both been shown to be independently associated with a decreased risk of developing coronary artery aneurysms. And although sex has not been shown to protect against coronary artery development, girls are less likely to have KD, with an occurrence ratio of 1 to 1.4 compared with boys.[10]

Our patient's presentation demonstrates some of the pitfalls that could lead to KD initially being disregarded in favor of another of diagnosis. Although though she had the classic findings of KD, her sex and race and the presence of bacterial pyuria were suggestive of another diagnosis. After the KD diagnosis had been made and the gold-standard therapy had been started, she continued to have fever, inflammation, and hemolytic anemia prior to symptom resolution. Even with her extended disease course, however, she never developed coronary artery abnormalities and recovered fully.

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